REMARKS

A. STATUS OF THE CLAIMS

Claims 1, 2 and 8-24 are pending, and claims 8-23 remain withdrawn as directed to nonelected subject matter. Claims 1, 2 and 24 are presently under active prosecution.

Claims 3-7 are previously canceled, without prejudice.

No new matter is added.

B. AMENDMENTS TO THE CLAIMS

No claims are amended.

C. CLAIM REJECTIONS UNDER 35 U.S.C. § 103(a)

At pages 3-5 of the Office Action, claims 1, 2 and 24 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Pedersen et al. ("Pedersen;" US 5,639,641) in view of Ramsland et al. The Examiner correctly notes that the previous respouse erroneously mentioned the reference identifier "Queen" in place of the reference identifier Ramsland. The cited art is fully addressed hereinbelow.

At page 6 of the Office Action, the Examiner has expanded on her previous reasoning in this rejection, quoting Pedersen, at Col. 28, lines 30-67. In particular, the Examiner has underlined and italicized the statement by Pedersen that the "two domains are then paired by least squares fitting on the most conserved strands of the antibody beta barrel..." The Examiner argues that "it is very well known in the art that said RMSD is calculated using a least-squares fitting." The Examiner concedes that the "mouse model was not produced crystallographically" but cites Ramsland as remedying this deficiency.

Applicants respectfully disagree. As explained in the previous Response the law requires that the claims must be considered as a whole, e.g., Manual of Patent Examining Procedure (MPEP) §2141.06(I). The MPEP explains that:

> In determining the differences between the prior art and the claims, the question under 35 U.S.C. 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 218 USPQ 871 (Fed. Cir.

1983); *Schenck v. Nortron Corp.*, 713 F.2d 782, 218 USPQ 698 (Fed. Cir. 1983). [Emphasis in original].

The Examiner's attention is respectfully directed to the disclosures of Pedersen, e.g., the Pedersen method steps at, e.g., Pedersen Cols. 5-6 and/or Pedersen claim 1, "a method for producing a humanized rodent antibody or fragment thereof by resurfacing, said method consisting essentially of..." reciting steps (a) through (i).

Based on the above, the Pedersen method requires:

> -that the heavy and light chain variable region framework surface exposed positions be selected because they are at least 98 % identical between rodent and human [step (a)];
>
> -that the heavy and light chain variable region framework surface exposed amino acid residues of the rodent antibody be substituted with the human ones [steps (b) through (d)];
>
> -further identifying amino acid residues that are within 5 Ångstroms of any atom of any residue of the complementarity determining regions of the rodent antibody [steps (e) through (f)];
>
> -that the further identified amino acid residues (that are within 5 Ångstroms...) be substituted back to the original rodent amino acid residue [steps (g) through (h)].

In addition, the Examiner's attention is respectfully directed to Pedersen at column 8, second paragraph, starting with, "[t]here are several key features of the resurfacing approach of the present invention..." and enumerating features (1) through (4). In particular, feature (2) of Pedersen requires assessing solvent accessibility. The instantly claimed invention does not require this step, and this step is submitted to be at odds with, and not a compatible fit with, steps (a) through (d) of instant claim 1.

As previously explained, Ramsland only mentions one instance where crystallographic investigation was applied to two pre-existing antibodies, *i.e.* humanized AF2 and mouse-human chimeric AF2. That study was designed to understand why the humanized antibody had a two-fold lower affinity for its target when compared to the chimeric antibody (p. 255, right column, second paragraph). Hence, Ramsland does not *a priori* use crystal structures for the selection of frameworks for the humanization process, but describes *a posteriori* determination of the crystal structures of pre-existing humanized and chimeric antibodies in order to understand their

characteristics. Thus, Ramsland employs *a posteriori* structural information to rationalize the reasons why an already performed humanization led to loss of affinity/specificity of the humanized version. Thus, at best, Ramsland teaches about the failures of others in the field.

The Examiner concedes that Pedersen does not teach a method wherein the rodent antibody molecular model has been determined by crystallographic methods. However, it is respectfully submitted that the difference goes beyond employing crystallographic methods. The instantly claimed invention is submitted to be a completely different process than the process that is recited by instant claim 1, et seq. The mere mention of crystallographic methods by Ramsland would have failed to teach or suggest the instantly claimed invention to the ordinary artisan, because nowhere are the specifically claimed process steps described or even hinted at.

The methods of claim 1, *et seq.*, require, in outline form:

> a) obtaining a crystallographic structure of the VH and VL regions of the animal antibody; ...
> b) pre-selecting a series of 0 to n possible framework acceptors of human origin or humanized antibodies, ...
> c) conducting a structural comparison between the VH and VL variable regions of the animal antibody and the VH and VL regions of the framework receptors of human origin...and
> - calculating for each comparison the root mean square deviation (RMS,Å), to identify the VH region and the VL region of human origin with the smaller RMS, in particular, the RMS is calculated between atoms of alpha carbon constituting the respective amino acid skeletons, not considering atom pairs with an RMS exceeding 2Å;
> d) inserting in appropriate position a CDR region of the animal antibody into the VH region and the VL region of human origin identified in c).

Thus, claim 1 requires five specific steps [step (c) comprises two steps] and any rejection of claim 1 must meet the legal burden to show how the cited reference(s) would have taught or suggested all of these five process steps, including the requirement of pre-selecting a series of 0 to n possible framework acceptors of human origin or humanized antibodies and the requirement that RMS is calculated between atoms of alpha carbon constituting the respective amino acid skeletons, not considering atom pairs with an RMS exceeding 2Å.

The Examiner's rebuttal, at page 6 of the Office Action, compares building the framework model of Pedersen to steps (b) and (c) of instant claim 1. However, nowhere in that comparison is it shown where Pedersen discloses step (b) of claim 1 ("pre-selecting a series of 0

to n possible framework acceptors..."). Further, nowhere in that comparison is it shown where Pedersen discloses key elements of step (c) of claim 1 ("the RMS is calculated between atoms of alpha carbon constituting the respective amino acid skeletons, not considering atom pairs with an RMS exceeding 2Å").

Thus, even if the skilled person would combine the teaching of Pedersen with Ramsland's s/he would not arrive at the claimed invention because so many features of the method of Pedersen would have to be replaced with features that are simply not disclosed in Ramsland.

Thus, it is respectfully urged that the Patent Office has failed to support a *prima facie* rejection based on the cited references, taken separately or in any combination.

For all of these reasons, it is respectfully requested that this ground of rejection be reconsidered and withdrawn.

D. DOUBLE PATENTING REJECTIONS

At pages 7-8 of the Office Action, the Examiner maintained the previous *provisional* rejection of claims 1, 2 and 24 as an alleged obviousness-type double patenting over claims 1, 2 and 24 of copending Appl. Ser. No. 12/838,062. Since there is not yet any indication of allowable subject matter in the instantly claimed invention, it is considered that this is a *provisional* rejection. Applicants acknowledge the *provisional* rejection, and respectfully ask to defer a response to this rejection until there is an indication of patentable subject matter in the instant patent application.

For all of these reasons, it is respectfully requested that this ground of rejection be reconsidered in any further Office Action.

E. CONCLUSION

It is respectfully submitted that the application is in condition for allowance, and reconsideration and allowance is hereby requested. If any questions remain, the Examiner is respectfully requested to contact the undersigned for a telephone interview, in the interest of expeditious prosecution.

F. **FEES**

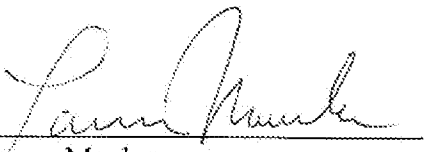
This response is timely filed. Thus, no fee is believed to be due. If, on the other hand, it is determined that any further fees are due or any overpayment has been made, the Assistant Commissioner is hereby authorized to debit or credit such sum to Deposit Account No. 02-2275.

Pursuant to 37 C.F.R. § 1.136(a)(3), please treat this and any concurrent or future reply in this application that requires a petition for an extension of time for its timely submission as incorporating a petition for extension of time for the appropriate length of time. The fee associated therewith is to be charged to Deposit Account No. 02-2275.

An early and favorable action on the merits is earnestly solicited.

Respectfully submitted,

LUCAS & MERCANTI, LLP

By: 

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